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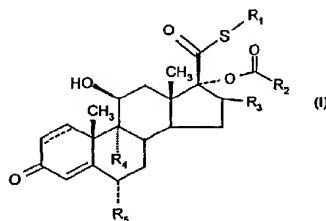
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(54) Title: ANTI-INFLAMMATORY 17.BETA.-CARBOTHIOATE ESTER DERIVATIVES OF ANDROSTANE WITH A CYCLIC ESTER GROUP IN POSITION 17.ALPHA



(57) Abstract: There are provided compound of formula (I) wherein R₁ represents C₁₋₆ alkyl or C₁₋₆ haloalkyl; R₂ represents C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl either of which may optionally be substituted by one or more groups selected from oxo, methyl, methylene and halogen; R₃ represents hydrogen, methyl (which may be in either the α or β configuration) or methylene; R₄ and R₅ are the same or different and each represents hydrogen or halogen; and (AA) represents a single or a double bond; and solvates thereof, processes for preparing them and their use in therapy.

ANTI-INFLAMMATORY 17.BETA.-CARBOTHIOATE ESTER DERIVATIVES OF ANDROSTANE
WITH A CYCLIC ESTER GROUP IN POSITION 17.ALPHA

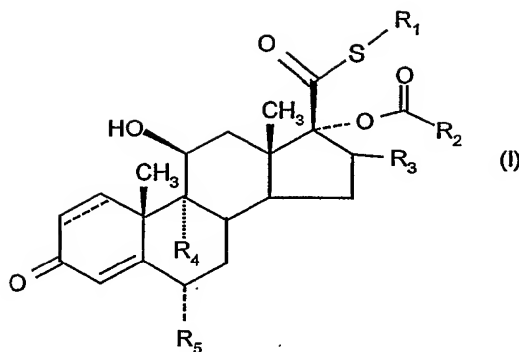
The present invention relates to novel anti-inflammatory and anti-allergic compounds of the androstane series and to processes for their preparation. The present invention also relates to pharmaceutical formulations containing the compounds and to therapeutic uses thereof, particularly for the treatment of inflammatory and allergic conditions.

Glucocorticoids which have anti-inflammatory properties are known and are widely used for the treatment of inflammatory disorders or diseases such as asthma and rhinitis. For example, US Patent 4335121 discloses 6α , 9α -Difluoro- 17α -(1-oxopropoxy)- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid S-fluoromethyl ester (known by the generic name of fluticasone propionate) and derivatives thereof. The use of glucocorticoids generally, and especially in children, has been limited in some quarters by concerns over potential side effects. The side effects that are feared with glucocorticoids include suppression of the Hypothalamic-Pituitary-Adrenal (HPA) axis, effects on bone growth in children and on bone density in the elderly, ocular complications (cataract formation and glaucoma) and skin atrophy. Certain glucocorticoid compounds also have complex paths of metabolism wherein the production of active metabolites may make the pharmacodynamics and pharmacokinetics of such compounds difficult to understand. Whilst the modern steroids are very much safer than those originally introduced it remains an object of research to produce new molecules which have excellent anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic properties, with an attractive side effect profile, and with a convenient treatment regime.

Certain novel androstane derivatives are disclosed in WO02/12265 and WO02/12266 (Glaxo Group), both of these documents being published after the earliest priority date of this patent application.

We have identified a novel series of glucocorticoids, which substantially meets these objectives.

Thus, according to one aspect of the invention, there is provided a compound of formula (I)



wherein

R_1 represents C_{1-6} alkyl or C_{1-6} haloalkyl;

- 5 R_2 represents C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl either of which may optionally be substituted by one or more groups selected from oxo, methyl, methylene and halogen;

R_3 represents hydrogen, methyl (which may be in either the α or β configuration) or methylene;

- 10 R_4 and R_5 are the same or different and each represents hydrogen or halogen; and

— represents a single or a double bond;

and solvates thereof.

Examples of solvates include hydrates.

- References hereinafter to a compound according to the invention includes
15 both compounds of formula (I) and solvates thereof.

It will be appreciated that the invention includes within its scope all stereoisomers (including enantiomers and diastereoisomers) of the compounds of formula (I) and mixtures thereof.

- Preferably, the absolute stereochemistry will be as shown in the
20 representation of compounds of formula (I).

Examples of C_{1-6} haloalkyl that R_1 may represent include C_{1-6} alkyl substituted by 1-3 halogen atoms, preferably 1 halogen atom. Preferred halogen atoms are selected from bromine, chlorine and fluorine.

- Examples of C_{3-8} cycloalkyl groups that R_2 may represent include cyclopropyl,
25 cyclobutyl, cyclopentyl and cyclohexyl and substituted derivatives such as methylcyclopropyl (eg 1-methylcyclopropyl or 2-methylcyclopropyl), dichlorocyclopropyl (eg 2,2-dichloropropyl), methyldichlorocyclopropyl (eg 1-methyl-2,2-dichlorocyclopropyl), exomethylenecyclobutyl (eg 3-exomethylenecyclobutyl),

tetramethylcyclopropyl (eg 2,2,3,3- tetramethylcyclopropyl) and methycyclobutyl (eg 1-methylcyclobutyl). Other examples include dimethylcyclobutyl (eg 3,3-dimethylcyclobutyl), difluorocyclobutyl (eg 3,3-difluorocyclobutyl), methylcyclopentyl (eg 1-methylcyclopentyl). A further example includes oxocyclobutyl (eg 3-oxo-cyclobutyl).

Examples of C₃₋₈ cycloalkenyl groups that R₂ may represent include alkenyl groups containing 1 or more double bonds (not being aromatic groups) such as cyclohexenyl eg cyclohex-2,3-enyl.

We prefer R₁ to represent fluoromethyl, chloromethyl, bromomethyl or 2'-fluoroethyl, especially fluoromethyl.

Preferably, R₂ represents C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl either of which may optionally be substituted by one or more groups selected from methyl, methylene and halogen. In an alternative aspect, R₂ represents C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl either of which may be substituted by oxo eg 3-oxocyclobutyl.

We prefer R₂ to represent C₃₋₈ cycloalkyl optionally substituted by one or more methyl and/or halogen groups. We particularly prefer R₂ to represent C₃₋₆ cycloalkyl, more preferably C₃₋₄ cycloalkyl, optionally substituted by one or more methyl or chlorine groups.

We also prefer R₂ to represent C₃₋₆ cycloalkyl substituted by methylene.

In one set of preferred compounds, R₂ is unsubstituted or substituted by at most one methyl or chlorine group. More preferably, R₂ is substituted by one methyl group, especially in the 1-position, eg 1-methyl cyclopropyl or 1-methyl-cyclobutyl.

In another set of preferred compounds, R₂ is substituted by more than one methyl group, eg 2,2,3,3- tetramethylcyclopropyl.

We prefer R₃ to represent methyl, especially methyl in the α configuration.

Compounds of formula (I) in which R₄ and R₅, which can be the same or different, each represents hydrogen, fluorine or chlorine, particularly hydrogen or fluorine, are preferred. Especially preferred are compounds in which both R₄ and R₅ are fluorine.

Preferably, $\text{---}\text{---}\text{---}\text{---}\text{---}$ represents a double bond.

It is to be understood that the present invention covers all combinations of particularly and preferred groups referred to hereinabove.

Preferred compounds of formula (I) include:

17 α -(Cyclobutylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;

- 17 α -(Cyclopentylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 17 α -(Cyclohexylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 5 17 α -(Cyclopropylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-
- 10 tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 17 α -(2,2-Dichloro-1-methycyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 17 α -(2,2-Dichlorocyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-
- 15 oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(3-methylenecyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(2-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 20 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-17 α -(3,3-dimethylcyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-17 α -(3,3-difluorocyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-
- 25 oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopentylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(3-oxocyclobutylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.
- 30 One particularly preferred compound is the following:
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Another particularly preferred compound is the following:

6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

Another particularly preferred compound is the following:

- 5 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester.

The compounds of formula (I) have potentially beneficial anti-inflammatory or anti-allergic effects, particularly upon topical administration, demonstrated by, for example, their ability to bind to the glucocorticoid receptor and to illicit a response via
10 that receptor with long lasting effect. Hence, the compounds of formula (I) are useful in the treatment of inflammatory and/or allergic disorders, especially in once-per-day therapy.

Examples of disease states in which the compounds of the invention have utility include skin diseases such as eczema, psoriasis, allergic dermatitis
15 neurodermatitis, pruritis and hypersensitivity reactions; inflammatory conditions of the nose, throat or lungs such as asthma (including allergen-induced asthmatic reactions), rhinitis (including hayfever), nasal polyps, chronic obstructive pulmonary disease, interstitial lung disease, and fibrosis; inflammatory bowel conditions such as ulcerative colitis and Crohn's disease; and auto-immune diseases such as
20 rheumatoid arthritis.

Compounds of the invention may also have use in the treatment of conjunctiva and conjunctivitis.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established conditions.

25 As mentioned above, compounds of formula (I) are useful in human or veterinary medicine, in particular as anti-inflammatory and anti-allergic agents, especially in once-per-day therapy.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable solvate thereof for use in human or
30 veterinary medicine, particularly in the treatment of patients with inflammatory and/or allergic conditions. Pharmaceutical compositions for once-per-day administration are of particular interest.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or physiologically acceptable solvate thereof for the

manufacture of a medicament for the treatment of patients with inflammatory and/or allergic conditions, especially for therapy once-per-day.

In a further or alternative aspect, there is provided a method for the treatment of a human or animal subject with an inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or physiologically acceptable solvate thereof, especially administration once-per-day.

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions comprising a compound of formula (I) or physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.

Further, there is provided a process for the preparation of such pharmaceutical compositions which comprises mixing the ingredients.

The compounds according to the invention may, for example, be formulated for oral, buccal, sublingual, parenteral, local or rectal administration, especially local administration.

Local administration as used herein, includes administration by insufflation and inhalation. Examples of various types of preparation for local administration include ointments, lotions, creams, gels, foams, preparations for delivery by transdermal patches, powders, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops), solutions/suspensions for nebulisation, suppositories, pessaries, retention enemas and chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) or liposome or microencapsulation preparations.

Advantageously compositions for topical administration to the lung include dry powder compositions and spray compositions.

Dry powder compositions for topical delivery to the lung may, for example, be presented in capsules and cartridges for use in an inhaler or insufflator of, for example, gelatine. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20µg-10mg of the compound of formula (I) optionally in combination with another active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit

dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Pharmaceutical formulations which are non-pressurised and adapted to be administered as a dry powder topically to the lung via the buccal cavity (especially those which are free of excipient or are formulated with a diluent or carrier such as lactose or starch, most especially lactose) are of particular interest.

Spray compositions may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosol composition may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. One example formulation is excipient free and consists essentially of (eg consists of) compound of formula (I) (preferably in unsolvated form eg as Form 1) (optionally in combination with another therapeutically active ingredient) and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixture thereof. Another example formulation comprises particulate compound of formula (I), a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixture thereof

and a suspending agent which is soluble in the propellant eg an oligolactic acid or derivative thereof as described in WO94/21229. The preferred propellant is 1,1,1,2-tetrafluoroethane. As noted elsewhere in this specification, compound of formula (I) does not appear to form a solvate with 1,1,1,2-tetrafluoroethane. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10 μ m, preferably 2-5 μ m. Particles having a size above 20 μ m are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of compound of formula (I) as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline, prepared for example by a process which comprises mixing in a continuous flow cell in the presence of ultrasonic radiation a flowing solution of compound of formula (I) as medicament in a liquid solvent with a flowing liquid antisolvent for said medicament (eg as described in International Patent Application PCT/GB99/04368) or else by a process which comprises admitting a stream of solution of the substance in a liquid solvent and a stream of liquid antisolvent for said substance tangentially into a cylindrical mixing chamber having an axial outlet port such that said streams are thereby intimately mixed through formation of a vortex and precipitation of crystalline particles of the substance is thereby caused (eg as described in International Patent Application PCT/GB00/04327). When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μ m and not less than 15% will have a MMD of less than 15 μ m.

Formulations for administration topically to the nose (eg for the treatment of rhinitis) include pressurised aerosol formulations and aqueous formulations administered to the nose by pressurised pump. Formulations which are non-pressurised and adapted to be administered topically to the nasal cavity are of particular interest. The formulation preferably contains water as the diluent or carrier for this purpose. Aqueous formulations for administration to the lung or nose may be provided with conventional excipients such as buffering agents, tonicity modifying

agents and the like. Aqueous formulations may also be administered to the nose by nebulisation.

Other possible presentations include the following:

5 Ointments, creams and gels, may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agent and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a solvent such as polyethylene glycol. Thickening agents and gelling agents which may be used according to the nature of the base include soft paraffin, aluminium stearate,
10 cetostearyl alcohol, polyethylene glycols, woolfat, beeswax, carboxypolymethylene and cellulose derivatives, and/or glyceryl monostearate and/or non-ionic emulsifying agents.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents,
15 suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents, suspending agents or preservatives.

20 Advantageously, the formulations of the invention may be buffered by the addition of suitable buffering agents.

The proportion of the active compound of formula (I) in the local compositions according to the invention depends on the precise type of formulation to be prepared but will generally be within the range of from 0.001 to 10% by weight. Generally,
25 however for most types of preparations advantageously the proportion used will be within the range of from 0.005 to 1% and preferably 0.01 to 0.5%. However, in powders for inhalation or insufflation the proportion used will be within the range of from 0.1 to 5%.

Aerosol formulations are preferably arranged so that each metered dose or
30 "puff" of aerosol contains 20 μ g-2000 μ g, preferably about 20 μ g-500 μ g of a compound of formula (I). Administration may be once daily or several times daily, for example 2, 3, 4 or 8 times, giving for example 1, 2 or 3 doses each time. The overall daily dose with an aerosol will be within the range 100 μ g-10mg preferably, 200 μ g-2000 μ g. The overall daily dose and the metered dose delivered by capsules and cartridges in an
35 inhaler or insufflator will generally be double those with aerosol formulations.

Topical preparations may be administered by one or more applications per day to the affected area; over skin areas occlusive dressings may advantageously be used. Continuous or prolonged delivery may be achieved by an adhesive reservoir system.

5 For internal administration the compounds according to the invention may, for example, be formulated in conventional manner for oral, parenteral or rectal administration. Formulations for oral administration include syrups, elixirs, powders, granules, tablets and capsules which typically contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, wetting agents, suspending
10 agents, emulsifying agents, preservatives, buffer salts, flavouring, colouring and/or sweetening agents as appropriate. Dosage unit forms are, however, preferred as described below.

Preferred forms of preparation for internal administration are dosage unit forms i.e. tablets and capsules. Such dosage unit forms contain from 0.1mg to 20mg
15 preferably from 2.5 to 10mg of the compounds of the invention.

The compounds according to the invention may in general may be given by internal administration in cases where systemic adreno-cortical therapy is indicated.

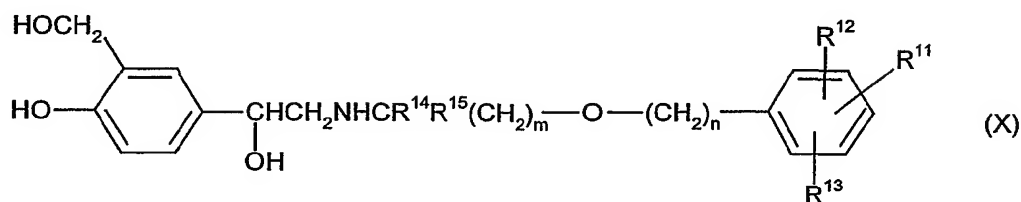
In general terms preparations, for internal administration may contain from 0.05 to 10% of the active ingredient dependent upon the type of preparation involved.
20 The daily dose may vary from 0.1mg to 60mg, e.g. 5-30mg, dependent on the condition being treated, and the duration of treatment desired.

Slow release or enteric coated formulations may be advantageous, particularly for the treatment of inflammatory bowel disorders.

The pharmaceutical compositions according to the invention may also be
25 used in combination with another therapeutically active agent, for example, a β_2 adrenoreceptor agonist, an anti-histamine or an anti-allergic. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable solvate thereof together with another therapeutically active agent, for example, a β_2 -adrenoreceptor agonist, an anti-histamine, an anti-
30 allergic or an anti-cholinergic.

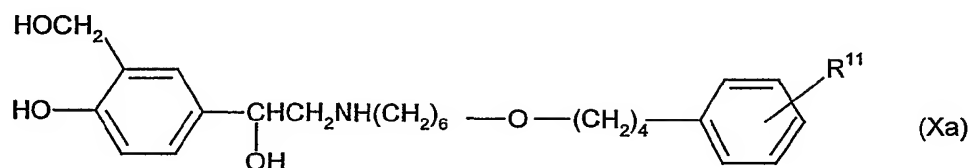
Examples of β_2 -adrenoreceptor agonists include salmeterol (eg as xinafoate), salbutamol (eg as sulphate), formoterol (eg as fumarate), fenoterol or terbutaline (eg as sulphate). Long-acting β_2 -adrenoreceptor agonists are preferred, especially those having a therapeutic effect over a 24 hour period.

Especially preferred long-acting β_2 -adrenoreceptor agonists are compounds of formula (X)



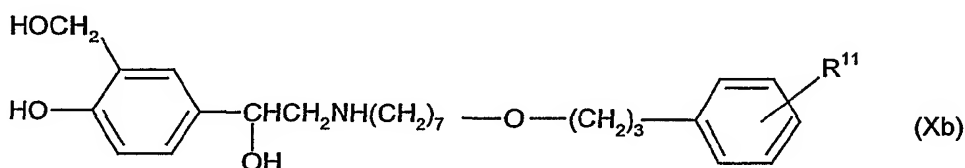
- 5 or a salt or solvate thereof, wherein:
 m is an integer of from 2 to 8;
 n is an integer of from 3 to 11, preferably from 3 to 7;
 with the proviso that m + n is 5 to 19, preferably 5 to 12;
 R¹¹ is -XSO₂NR¹⁶R¹⁷
- 10 wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;
 R¹⁶ and R¹⁷ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C(O)NR¹⁸R¹⁹, phenyl, and phenyl (C₁₋₄alkyl)-, or R¹⁶ and R¹⁷, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring, and R¹⁶ and R¹⁷ are each optionally substituted
- 15 by one or two groups selected from halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy, -CO₂R¹⁸, -SO₂NR¹⁸R¹⁹, -CONR¹⁸R¹⁹, -NR¹⁸C(O)R¹⁹, or a 5-, 6- or 7-membered heterocyclic ring;
 R¹⁸ and R¹⁹ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and
- 20 p is an integer of from 0 to 6, preferably from 0 to 4;
 R¹² and R¹³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and C₁₋₆haloalkyl; and
 R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R¹⁴ and R¹⁵ is not more than 4.
- 25 In the compounds of formula (I) the group R¹¹ is preferably attached to the meta-position relative to the -O-(CH₂)_n- link.
 R¹¹ preferably represents -SO₂NR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from hydrogen and C₁₋₆alkyl, more preferably R¹¹ is -SO₂NH₂.
 R¹⁴ and R¹⁵ are preferably independently selected from hydrogen and methyl, more preferably R¹⁴ and R¹⁵ are both hydrogen.
- 30 m is suitably 4, 5, or 6, and n is suitably 3, 4, 5 or 6. Preferably m is 5 or 6 and n is 3 or 4, such that m + n is 8, 9 or 10, preferably 9.

More especially preferred compounds of formula (X) are compounds of formula (Xa)



- 5 or a salt or solvate thereof, wherein
R¹¹ is as defined above for formula (X).

Further more especially preferred compounds of formula (X) are compounds of formula (Xb):



- 10 or a salt or solvate thereof, wherein
R¹¹ is as defined above for formula (X).

In the compounds of formulae (Xa) and (Xb), the group R¹¹ is preferably attached to the meta-position relative to the -O-(CH₂)_n-, -O-(CH₂)₄- or -O-(CH₂)₃- link respectively.

In the compounds of formulae (Xa) and (Xb), R¹¹ is preferably -SO₂NR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from hydrogen and C₁₋₆alkyl, more preferably R¹¹ is -SO₂NH₂.

In the definition of R¹¹ where 'R¹⁶ and R¹⁷ together with the nitrogen atom to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring', the term "5-, 6-, or 7- membered nitrogen containing ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes the sulfonamide nitrogen atom and optionally 1 or 2 other heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, and piperazinyl.

In the definition of R¹¹, specifically the optional substituents on R¹⁶ and R¹⁷, the term "5-, 6-, or 7- membered heterocyclic ring" means a 5-, 6-, or 7- membered fully or partially saturated or unsaturated ring which includes 1, 2, 3 or 4 heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of

such a ring include pyrrolyl, furyl, thienyl, pyridinyl, pyrazinyl, pyridazinyl, imidazolyl, tetrazolyl, tetrahydrofuranyl, oxazolyl, thiazolyl, thiadiazolyl, piperidinyl, morpholinyl, and piperazinyl.

In the definition of X, the term "alkenylene" includes both *cis* and *trans* structures. Suitable examples of alkenylene groups include -CH=CH-.

The compounds of formulae (X), (Xa) and (Xb) include an asymmetric centre, namely the carbon atom of the



group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions.

Similarly, where R¹⁴ and R¹⁵ are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formulae (X), (Xa) and (Xb) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

The most preferred compound of formula (X) is 3-(4-([6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl]oxy)butyl)benzenesulfonamide or a salt or solvate thereof.

Salts and solvates of compounds of formulae (X), (Xa) and (Xb) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formulae (X), (Xa) and (Xb) and their pharmaceutically acceptable salts and solvates.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballic, cinnamic, substituted cinnamic (for example, phenyl,

methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

10

Compounds of formula (X), (Xa) and (Xb) may be prepared by reference to Example X recited below, by analogous processes, or by other conventional processes known *per se*.

15

Since the compounds of formula (I) are long-acting, preferably the composition comprising the compound of formula (I) and the long-acting β_2 -adrenoreceptor agonists will be delivered once-per-day and the dose of each will be selected so that the composition has a therapeutic effect in the treatment of respiratory disorders effect (eg in the treatment of asthma or COPD, particularly asthma) over 24 hours or more.

20

Examples of anti-histamines include methapyrilene or loratadine. Examples of anti-allergics include cromoglycate (eg as sodium), ketotifen and nedocromil (as as sodium). Examples of anti-cholinergics include ipratropium (eg as bromide), tiotropium, atropine or oxitropium. Any of the aforementioned substances may be employed in the form of alternative salts or solvates thereof.

25

Other suitable combinations include, for example, other anti-inflammatory agents eg. NSAIDs (eg. PDE4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists)) or antiinfective agents (eg. antibiotics, antivirals).

30

Of particular interest is use of the compounds of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds

35

rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4. Initial experiments were conducted to establish and validate a [3H]-rolipram binding assay. Details of this work are given in the Binding Assays described in detail below.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [3H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μ M [3H]-cAMP as the substrate.

Examples of useful PDE4 inhibitors are:

(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-
isothioureido]benzyl)-2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
(R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(-)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-

cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or greater.

5 Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3- (cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also
10 known as cilomast) and its salts, esters, pro-drugs or physical forms;
AWD-12-281 from Astra (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787; Parke-Davis/Warner-Lambert); a
15 benzodioxole derivative Kyowa Hakko disclosed in WO 9916766; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12(Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO 9947505) from Byk-Gulden; or a compound identified as T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998,
20 284(1): 162).

Phosphodiesterase and Rolipram Binding Assays

Assay method 1A

Isolated human monocyte PDE4 and hrPDE (human recombinant PDE4) was determined to exist primarily in the low affinity form. Hence, the activity of test
25 compounds against the low affinity form of PDE4 can be assessed using standard assays for PDE4 catalytic activity employing 1 μ M [³H]cAMP as a substrate (Torphy et al., J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992).

Rat brain high speed supernatants were used as a source of protein and both enantiomers of [³H]-rolipram were prepared to a specific activity of 25.6 Ci/mmol.
30 Standard assay conditions were modified from the published procedure to be identical to the PDE assay conditions, except for the last of the cAMP: 50mM Tris HCl (pH 7.5), 5 mM MgCl₂, 50 μ M 5'-AMP and 1 nM of [³H]-rolipram (Torphy et al., J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992). The assay was run for 1 hour at 30° C. The reaction was terminated and bound ligand was separated from free
35 ligand using a Brandel cell harvester. Competition for the high affinity binding site

was assessed under conditions that were identical to those used for measuring low affinity PDE activity, expect that [^3H]-cAMP was not present.

Assay method 1B

Measurement of Phosphodiesterase Activity

- 5 PDE activity was assayed using a [^3H]cAMP SPA or [^3H]cGMP SPA enzyme assay as described by the supplier (Amersham Life Sciences). The reactions were conducted in 96-well plates at room temperature, in 0.1 ml of reaction buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 8.3 mM MgCl_2 , 1.7 mM EGTA, [^3H]cAMP or [^3H] cGMP (approximately 2000 dpm/pmol), enzyme and
10 various concentrations of the inhibitors. The assay was allowed to proceed for 1 hr and was terminated by adding 50 μl of SPA yttrium silicate beads in the presence of zinc sulfate. The plates were shaken and allowed to stand at room temperature for 20 min. Radiolabeled product formation was assessed by scintillation spectrometry.

[^3H]R-rolipram binding assay

- 15 The [^3H]R-rolipram binding assay was performed by modification of the method of Schneider and co-workers, see Nicholson, *et al.*, Trends Pharmacol. Sci., Vol. 12, pp.19-27 (1991) and McHale *et al.*, Mol. Pharmacol., Vol. 39, 109-113 (1991). R-Rolipram binds to the catalytic site of PDE4 see Torphy *et al.*, Mol. Pharmacol., Vol. 39, pp. 376-384 (1991). Consequently, competition for [^3H]R-rolipram binding
20 provides an independent confirmation of the PDE4 inhibitor potencies of unlabeled competitors. The assay was performed at 30°C for 1 hr in 0.5 μl buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 5 mM MgCl_2 , 0.05% bovine serum albumin, 2 nM [^3H]R-rolipram (5.7×10^4 dpm/pmol) and various concentrations of non-radiolabeled inhibitors. The reaction was stopped by the addition of 2.5 ml of
25 ice-cold reaction buffer (without [^3H]-R-rolipram) and rapid vacuum filtration (Brandel Cell Harvester) through Whatman GF/B filters that had been soaked in 0.3% polyethylenimine. The filters were washed with an additional 7.5 ml of cold buffer, dried, and counted via liquid scintillation spectrometry.

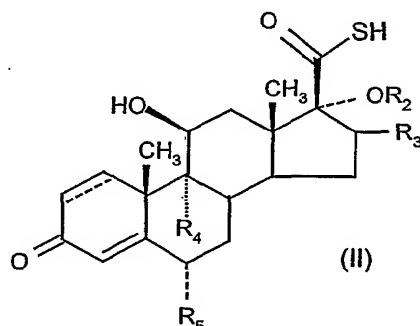
- The invention thus provides, in a further aspect, a combination comprising a
30 compound of formula (I) or a physiologically acceptable solvate thereof together with a PDE4 inhibitor.

- The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically
35 acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

- 5 The compounds of formula (I) and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

A process according to the invention for preparing a compound of formula (I) comprises alkylation of a thioacid of formula (II)

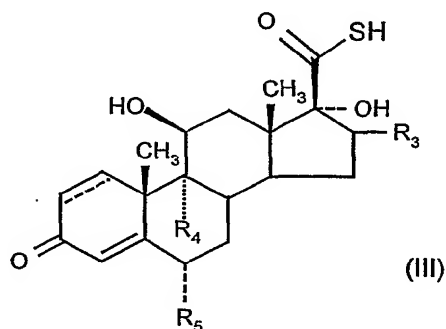


wherein R^2 , R^3 , R^4 , R^5 and --- are as defined above.

- 10 In this process the compound of formula (II) may be reacted with, for example, an appropriate alkyl or haloalkyl halide under standard conditions.

When R_1 represents fluoromethyl, the preferred haloalkyl halide reagent is bromofluoromethane.

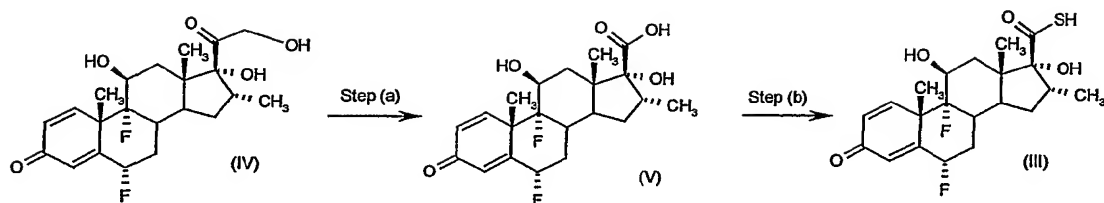
- Compounds of formula (II) may be prepared from the corresponding 17α -
15 hydroxyl derivative of formula (III):



- wherein R^2 , R^3 , R^4 , R^5 and --- are as defined above, using for example, the methodology described by G. H. Phillipps *et al.*, (1994) *Journal of Medicinal Chemistry*, **37**, 3717-3729. For example the compound of formula (III) may be
20 reacted with a compound of formula $R_2\text{COOH}$ or an activated derivative thereof eg an activated ester, anhydride or halide (eg the acid chloride). The reaction may be

performed in the presence of an organic solvent eg triethylamine, usually together with dimethylaminopyridine (DMAP).

Compounds of formula (III) may be prepared in accordance with procedures described in GB 2088877B. Compounds of formula (III) may also be prepared by a
5 process comprising the following steps:



Step (a) comprises oxidation of a solution containing the compound of formula (IV). Preferably, step (a) will be performed in the presence of a solvent comprising methanol, water, tetrahydrofuran, dioxan or diethylene glycol dimethylether. For example, so as to enhance yield and throughput, preferred solvents are methanol, water or tetrahydrofuran, and more preferably are water or tetrahydrofuran, especially water and tetrahydrofuran as solvent. Dioxan and diethylene glycol dimethylether are also preferred solvents which may optionally (and preferably) be employed together with water. Preferably, the solvent will be present in an amount of between 3 and 10vol relative to the amount of the starting material (1wt.), more preferably between 4 and 6 vol., especially 5 vol. Preferably the oxidising agent is present in an amount of 1-9 molar equivalents relative to the amount of the starting material. For example, when a 50% w/w aqueous solution of periodic acid is employed, the oxidising agent may be present in an amount of between 1.1 and 10wt. relative to the amount of the starting material (1wt.), more preferably between 1.1 and 3wt., especially 1.3wt. Preferably, the oxidation step will comprise the use of a chemical oxidising agent. More preferably, the oxidising agent will be periodic acid or iodic acid or a salt thereof. Most preferably, the oxidising agent will be periodic acid or sodium periodate, especially periodic acid. Alternatively (or in addition), it will also be appreciated that the oxidation step may comprise any suitable oxidation reaction, eg. one which utilises air and/or oxygen. When the oxidation reaction utilises air and/or oxygen, the solvent used in said reaction will preferably be methanol. Preferably, step (a) will involve incubating the reagents at room temperature or a little warmer, say around 25 °C eg for 2 hours. The compound of formula (V) may be isolated by recrystallisation from the reaction mixture by addition of an anti-solvent. A suitable anti-solvent for compound of formula (V) is water. Surprisingly we have discovered that it is highly desirable to control the conditions under which the compound of formula (V) is precipitated by addition of anti-solvent eg water. When the recrystallisation is performed using chilled water (eg water/ice mixture at a temperature of 0-5 °C) although better anti-solvent properties may be expected we have found that the

crystalline product produced is very voluminous, resembles a soft gel and is very difficult to filter. Without being limited by theory we believe that this low density product contains a large amount of solvated solvent within the crystal lattice. By contrast when conditions of around 10 °C or higher are used (eg around ambient temperature) a granular product of a sand like consistency which is very easily filtered is produced. Under these conditions, crystallisation typically commences after around 1 hour and is typically completed within a few hours (eg 2 hours). Without being limited by theory we believe that this granular product contains little or no of solvated solvent within the crystal lattice.

Step (b) will typically comprise the addition of a reagent suitable for converting a carboxylic acid to a carbothioic acid eg. using hydrogen sulphide gas together with a suitable coupling agent eg. carbonyldiimidazole (CDI) in the presence of a suitable solvent eg. dimethylformamide.

Solvates of compounds of formula (I) which are not physiologically acceptable may be useful as intermediates in the preparation of compounds of formula (I) or physiologically acceptable solvates thereof.

The advantages of compounds of formula (I) and/or solvates thereof may include the fact that the substances appear to demonstrate excellent anti-inflammatory properties, with predictable pharmacokinetic and pharmacodynamic behaviour, with an attractive side-effect profile (demonstrated for example, by increased selectivity for the glucocorticoid receptor over the progesterone receptor and/or increased selectivity for glucocorticoid receptor mediated transrepression over transactivation) and are compatible with a convenient regime of treatment in human patients. Further advantages may include the fact that the substances have desirable physical and chemical properties which allow for ready manufacture and storage.

The following non-limiting Examples illustrate the invention:

EXAMPLES

General

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Intermediates

Intermediate 1: 17 α -(Cyclobutylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

A solution of 6 α ,9 α -difluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid (prepared in accordance with the procedure described in GB 2088877B) (1g, 2.42mmol) in anhydrous dichloromethane (20ml) and triethylamine (0.88ml, 6.32mmol) was treated at <5 °C under nitrogen with a solution of cyclobutanecarbonyl chloride (0.72ml, 6.31mmol) in anhydrous dichloromethane (5ml) over approximately 2min. The solution was stirred at <5 °C for 45min and then diluted with dichloromethane (20ml) and washed successively with 5% sodium hydrogen carbonate solution (20ml), 1M hydrochloric acid (20ml) and water (20ml). The organic solution was dried (Na₂SO₄) and evaporated to give an off-white foam (1.47g) which was dissolved in acetone (30ml) and treated with 1-methylpiperazine (1ml, 9mmol). After 2.5h the solution was slowly added to a stirred mixture of 2M hydrochloric acid (55ml) and ice (55ml) and the precipitate was collected and dried in vacuo to give the title compound as a white solid (1.12g, 93.5%): LCMS retention time 3.79min, *m/z* 495 MH⁺

Intermediate 2: 17 α -(Cyclopentylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid.

Prepared using methods similar to that described for Intermediate 1.
LCMS retention time 4.00min, *m/z* 509 MH⁺

Intermediate 3: 17 α -(Cyclohexylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.
LCMS retention time 4.17min, *m/z* 523 MH⁺

Intermediate 4: 17 α -(Cyclopropylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.
LCMS retention time 3.65min, *m/z* 481 MH⁺

Intermediate 5: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.
LCMS retention time 3.75min, *m/z* 495 MH⁺

Intermediate 6: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.12min, m/z 537 MH⁺

- 5 Intermediate 7: 17 α -(2,2-Dichloro-1-methylcyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.20min, m/z 563,565 MH⁺

- 10 Intermediate 8: 17 α -(2,2-Dichlorocyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.14min, m/z 549,551 MH⁺

Intermediate 9: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(3-methylenecyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

- 15 Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.10min, m/z 507 MH⁺

Intermediate 10: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(2-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

- 20 LCMS retention time 3.90min, m/z 495 MH⁺

Intermediate 11: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.13min, m/z 509 MH⁺

- 25 Intermediate 12: 6 α ,9 α -Difluoro-17 α -(3,3-dimethylcyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.09min, m/z 523 MH⁺

- 30 Intermediate 13: 6 α ,9 α -Difluoro-17 α -(3,3-difluorocyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 3.78min, m/z 531 MH⁺

Intermediate 14: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopentylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid

Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 4.05min, m/z 523 MH⁺

Intermediate 15: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(3-oxocyclobutylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid

- 5 Prepared using methods similar to that described for Intermediate 1.

LCMS retention time 3.41min, m/z 509 MH⁺

Examples

Example 1: 17 α -(Cyclobutylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

- 10 Sodium hydrogen carbonate (112mg, 1.33mmol) was added to a solution of Intermediate 1 (600mg, 1.21mmol) in anhydrous N,N-dimethylformamide (6ml) and the mixture cooled to -20 °C under nitrogen. Bromofluoromethane (0.15ml, 2.7mmol) was added and the mixture was stirred at -20 °C for 2h. Diethylamine (0.6ml, 5.8mmol) was added and the mixture stirred at -20 °C for 15min and then added to
- 15 vigorously stirred 2M hydrochloric acid (25ml). Water (75ml) was added and after stirring for a further 30min the white precipitate was collected and dried in vacuo (606mg). This material was purified by column chromatography on silica gel to give the title compound as a white solid (520mg, 81%): LCMS retention time 3.67min, m/z 527 MH⁺.

- 20 Example 2: 17 α -(Cyclopentylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 2 using methods similar to that described for Example 1
LCMS retention time 3.92min, m/z 541 MH⁺

- Example 3: 17 α -(Cyclohexylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester
- 25

Prepared from Intermediate 3 using methods similar to that described for Example 1
LCMS retention time 4.02min, m/z 555 MH⁺

Example 4: 17 α -(Cyclopropylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

- 30 Prepared from Intermediate 4 using methods similar to that described for Example 1
LCMS retention time 3.54min, m/z 513 MH⁺

Example 5: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 5 using methods similar to that described for Example 1
LCMS retention time 3.66min, m/z 527 MH⁺

Example 6: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 6 using methods similar to that described for Example 1
LCMS retention time 4.02min, m/z 569 MH⁺

Example 7: 17 α -(2,2-Dichloro-1-methylcyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 7 using methods similar to that described for Example 1
LCMS retention time 3.79min, m/z 595,597,599 MH⁺

Example 8: 17 α -(2,2-Dichlorocyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 8 using methods similar to that described for Example 1
LCMS retention time 3.68min, m/z 581,583 MH⁺

Example 9: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(3-methylenecyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 9 using methods similar to that described for Example 1
LCMS retention time 3.68min, m/z 539 MH⁺

Example 10: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(2-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 10 using methods similar to that described for Example 1.
LCMS retention time 3.57min, m/z 527 MH⁺

Example 11: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclobutylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Prepared from Intermediate 11 using methods similar to that described for Example 1.
LCMS retention time 3.73min, m/z 541 MH⁺

Example 12: 6 α ,9 α -Difluoro-17 α -(3,3-dimethylcyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester

Water (1.8ml), benzyltributylammonium chloride (35mg) and diisopropylethylamine (0.21ml) were added to a stirred and cooled (0 °C) solution of Intermediate 12 (585mg, 1.12mmol) in ethyl acetate (15ml). A solution of bromofluoromethane (0.075ml) in ethyl acetate (0.75ml) was added and the mixture stirred at room temperature for 18h. A solution of 2% diethylamine in 4:1 acetonitrile:water (1ml) was added and the mixture stirred for 10min. The organic phase was separated, washed successively with 0.5M hydrochloric acid, water and 1% sodium bicarbonate solution and dried and evaporated. The residue (570mg) was purified by preparative HPLC to give the title compound as a cream solid (490mg, 79%): LCMS retention time 3.75min, m/z 555 MH^+ .

Example 13: 6 α ,9 α -Difluoro-17 α -(3,3-difluorocyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester
Prepared from Intermediate 13 using methods similar to that described for Example 12. LCMS retention time 3.47min, m/z 563 MH^+

Example 14: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopentylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester
Prepared from Intermediate 14 using methods similar to that described for Example 12. LCMS retention time 3.71min, m/z 555 MH^+

Example 15: 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(3-oxocyclobutylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester
Prepared from Intermediate 15 using methods similar to that described for Example 12. LCMS retention time 3.24min, m/z 541 MH^+

Preparation of long acting β_2 -adrenoreceptor agonist

Example X: 3-(4-([6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)-hexyl]oxy)butyl)benzenesulfonamide acetate
i) Di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate
Cesium carbonate (70.4g) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone, (Glaxo, DE 3513885, 1985) (61.8g) and di-*t*-butyl iminodicarboxylate (47.15g) in acetonitrile (600ml) under nitrogen. After vigorous stirring at 21°C for 24 h the mixture was diluted with water (ca800ml) and the product was extracted with diethyl ether (1litre, then 200ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to ca400ml.
The white crystals were collected by filtration, washed with diethyl ether and dried to

give the *title compound* (24.4g) δ (CDCl_3) 7.78(1H, dd, J 8, 2Hz), 7.65 (1H, brs), 6.87(1H, d, J 8Hz), 4.97(2H, s), 4.88(2H, s), 1.56(6H, s) and 1.48 (18H, s). Further concentration of the mother liquors gave additional product (13.8g). A third crop (7.1g) was obtained by chromatographing the mother liquors on silica gel,

5 evaporating the appropriate eluate and triturating with diethyl ether.

ii) tert-Butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate

Trifluoroacetic acid (92ml) was added to a stirred solution of di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate, (352.55g) in dichloromethane (3.6litres) at 21°C and the reaction was stirred for 1.5 h. Aqueous NaOH solution (1.75litres) was added and after 10 min the phases were separated. The organic layer was washed with water, dried (MgSO_4) and evaporated to an oil. This was stored under high vacuum overnight and then triturated with hexane:ether (3:1) to give the crude product (226.61g). This was purified by recrystallisation from diethyl ether to give the *title compound* (122.78g). Further product (61.5g) was obtained from the mother liquors by evaporation and chromatography on a Biotage using 15% ethyl acetate in hexane. LCMS RT = 3.37min.

iii) tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate

A 2M solution of borane - dimethyl sulphide in THF (28ml) was added slowly to a 1M solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (56ml) at 0°C under nitrogen. A solution of tert-butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate, (108.2g) in THF (1.3litres) was added slowly keeping the temperature below 5°C followed by 2M solution of borane - dimethyl sulphide in THF (252ml) over 50 min. After 1 h, 2M HCl (170ml) was added with cooling and the mixture was partitioned between ethyl acetate and water. The organic layer was washed with saturated NaHCO_3 solution and brine and dried (MgSO_4). The solution was concentrated and the product purified by chromatography on flash silica gel (800g), eluting successively with hexane:ethyl acetate (4:1 then 3:1) to give the *title compound* (93.3g), LCMS RT = 3.31min.

iv) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate, (86.37g) in DMF (600ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 11.9g) in DMF (160ml) with cooling such that the internal temperature remained at 0°C under nitrogen. The mixture was stirred at 21°C for 2 h. The mixture was recooled to 0°C and 2M HCl (134ml) was added. The mixture

was diluted with water and the product was extracted with ethyl acetate twice. The solution was washed with brine twice, dried (MgSO₄) and evaporated to give the *title compound* (63.55g) LCMS RT = 2.66min.

v) 6-Bromohexyl but-3-ynyl ether

- 5 3-Butyn-1-ol (42.4ml) was stirred vigorously with 1,6-dibromohexane (260ml) and tetrabutylammonium bisulphate (2.4g) in 50% aqueous sodium hydroxide solution (200ml) under nitrogen for 3 days. Water (ca 700ml) was added and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane (2 × 100ml) and the combined organic layers were washed with water, dried (MgSO₄)
10 and concentrated. The residue in petroleum ether (bp 40 - 60°) was loaded onto a column of silica gel (1.5kg) and the column was eluted with petroleum ether (bp 40 - 60°C), then 10% diethyl ether in petroleum ether (bp 40 - 60°C) to give the *title compound* (103.3g), δ (CDCl₃) 3.56(2H, t, J 7Hz), 3.47(2H, t, J 7Hz), 3.42(2H, t, J 7Hz), 2.45(2H, m), 1.99(1H, t, J 2Hz), 1.87(2H, m), 1.60(2H, m) and 1.50 to 1.33 (4H, m).
15 m).

vi) (5R)-3-[6-(But-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

- (5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (10g) in DMF (100ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 2.33g) in DMF (50ml) with stirring under nitrogen and maintaining the
20 internal temperature at 0°C. Stirring was continued at 0 - 5°C for 1 h. The mixture was recooled to 0°C and a solution of 6-bromohexyl but-3-ynyl ether (14.7g) in DMF (50ml) was added over 1 min. The mixture was then stirred at 20 - 30°C for 2 h. 2M HCl (9ml) was added and the mixture was partitioned between water and diethyl
25 ether. The aqueous layer was extracted with more diethyl ether and the combined organic layers were washed twice with brine. After drying (MgSO₄) the solution was concentrated and loaded onto a column of silica gel (600g) set up in diethyl ether: petroleum ether (bp 40 - 60°C) (1:2). The column was eluted successively with this mixture, then (1:1) and then diethyl ether to give the *title compound* (13.88g) LCMS
30 RT = 3.45min.

vii) 3-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)but-1-ynyl]benzenesulfonamide

- (5R)-3-[6-(But-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (1.79g) was stirred with 3-iodobenzene sulphonamide (1.4g) in
35 acetonitrile:triethylamine (1:1, 42ml) under nitrogen for 10 min. Cuprous iodide

(0.083g) and dichlorobis(triphenylphosphine)palladium (0.192g) were added and the mixture was stirred for 17 h under nitrogen at 21°C. The mixture was evaporated to dryness and the residue was chromatographed on silica gel (250g) in 30% ethyl acetate: petroleum ether (bp 40 - 60°), then 50%, then 75% and finally ethyl acetate to give the *title compound* (2.35g), LCMS RT = 3.44min.

viii) 3-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]benzenesulfonamide

3-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)but-1-ynyl]benzenesulfonamide (2.35g) was stirred with platinum oxide (0.3g) in THF (30ml) under hydrogen for 2 h. The catalyst was removed by filtration using a filter aid and the filter cake was leached with ethyl acetate. The combined filtrates were passed through silica gel (200g) in ethyl acetate and the eluate was evaporated to give the *title compound* (2.32g), LCMS RT = 3.49min.

ix) 3-[4-({6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl]benzenesulfonamide

3-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]benzenesulfonamide (0.43g) was stirred in THF (10ml) while purging with a vigorous stream of nitrogen for 5 min. Potassium trimethylsilanoate (0.43g) was added and the mixture was stirred at 70°C under nitrogen for 2.5 h. The mixture was partitioned between dichloromethane and pH 6.4 phosphate buffer and the aqueous layer was extracted with more dichloromethane. The combined organic layers were washed with water, dried (MgSO₄) and concentrated. The residue was purified on silica gel (60g), eluting successively with ethyl acetate:petroleum ether (bp 40 - 60°C) (1:1), ethyl acetate, 10% then 20% methanol in ethyl acetate to give the *title compound* (0.286g), LCMS RT = 2.56min.

x) 3-[4-({6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)-hexyl}oxy)butyl]benzenesulfonamide acetate

3-[4-({6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl]benzenesulfonamide (0.283g) was stirred with acetic acid (8ml) and water (4ml) at 70° for 35 min before evaporating to dryness. The residue was re-evaporated twice with toluene to give the *title compound* (0.318g) LCMS RT = 2.34min, ES +ve 495 (MH)⁺.

Pharmacological Activity

Pharmacological activity was assessed in a functional in vitro assay of glucocorticoid agonist activity which is generally predictive of anti-inflammatory or anti-allergic activity in vivo.

The functional assay was based on that described by K.P.Ray et al., Biochem J. (1997), **328**, 707-715. A549 cells stably transfected with a reporter gene containing the NF- κ B responsive elements from the ELAM gene promoter coupled to sPAP (secreted alkaline phosphatase) were treated with test compounds at appropriate doses for 1 hour at 37°C. The cells were then stimulated with tumour necrosis factor (TNF, 10ng/ml) for 16 hours, at which time the amount of alkaline phosphatase produced is measured by a standard colourimetric assay. Dose response curves were constructed from which EC₅₀ values were estimated.

In this test the compounds of Examples 1 to 15 showed an EC₅₀ value of <2nM.

Screen for progesterone receptor activity

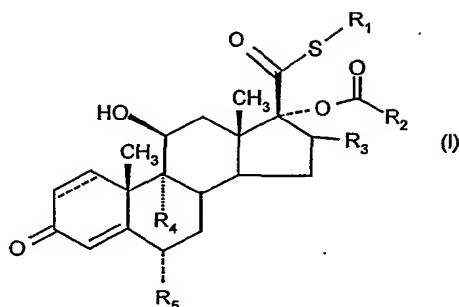
The human breast cancer cell line T47D has been reported to upregulate an endogenous alkaline phosphatase in response to progestins (Di Lorenzo et al., Cancer Research (1991) **51**, 4470-4475. T47D cells were seeded into 96 well plates at a density of 1×10^5 cells per well and grown overnight at 37°C. Steroids were dissolved in DMSO, added to the cells (final DMSO concentration 0.7%), and incubated for 24 hours at 37°C. The cells were then washed with PBS and lysed with RIPA buffer (1% IGEPAL, 0.5% Na deoxycholate, 0.1% SDS in phosphate buffered saline). Alkaline phosphatase activity was measured spectrophotometrically (405nm) using p-nitrophenylphosphate (1.5mg/ml) as a substrate dissolved in 1M diethanolamine, 0.28M NaCl, 0.5mM MgCl₂. Dose response curves were constructed from which EC₅₀ values were estimated.

Examples 5 and 11 were tested for progesterone activity in accordance with the above screen and the selectivity was determined by dividing the ED₅₀ at the progesterone receptor by the ED₅₀ at the glucocorticoid receptor. The selectivity of Example 5 was 353 (compare fluticasone propionate: selectivity = 57) and of Example 11 was 1230 (compare fluticasone propionate: selectivity = 107).

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps. The patents and patent applications described in this application are herein incorporated by reference.

CLAIMS

1. A compound of formula (I)



5 wherein

R_1 represents C_{1-6} alkyl or C_{1-6} haloalkyl;

R_2 represents C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl either of which may optionally be substituted by one or more groups selected from oxo, methyl, methylene and halogen;

10 R_3 represents hydrogen, methyl (which may be in either the α or β configuration) or methylene;

R_4 and R_5 are the same or different and each represents hydrogen or halogen; and

— represents a single or a double bond;

and solvates thereof.

15 2. A compound according to claim 1 in which R_2 represents C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl either of which may optionally be substituted by one or more groups selected from methyl, methylene and halogen.

3. A compound according to claim 1 or claim 2 in which R_2 represents C_{3-6} cycloalkyl optionally substituted by one or more methyl and/or chlorine groups.

20 4. A compound according to any one of claims 1 to 3 in which R_1 represents fluoromethyl, chloromethyl, bromomethyl or 2'-fluoroethyl.

5. A compound according to claim 4 in which R_1 represents fluoromethyl.

6. A compound according to any one of claims 1 to 5 in which R_3 is methyl.

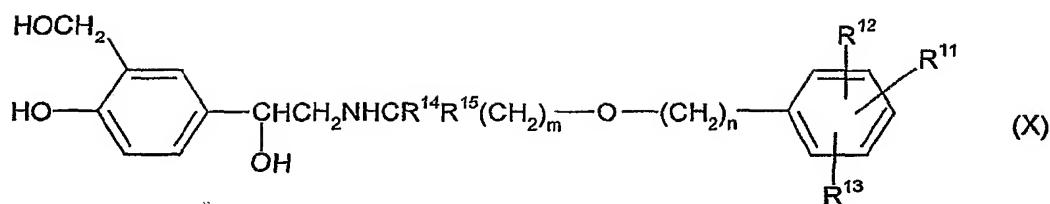
25 7. A compound according to any of claims 1 to 6 in which R_4 and R_5 are the same or different and each represents hydrogen, fluorine or chlorine.

8. A compound according to claim 7 in which R_4 and R_5 are the same or different and each represents hydrogen or fluorine.

9. A compound according to claim 8 in which both R_4 and R_5 are fluorine.

10. A compound according to any one of claims 1 to 9 in which \equiv represents a double bond.
11. A compound according to claim 1 which is:
- 17 α -(Cyclobutylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-
 5 androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 17 α -(Cyclopentylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-
 androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 17 α -(Cyclohexylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-
 androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 10 17 α -(Cyclopropylcarbonyl)oxy- 6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-oxo-
 androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 or a solvate of any one thereof.
12. A compound according to claim 1 which is:
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methycyclopropylcarbonyl)
 15 oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(2,2,3,3-
 tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-
 fluoromethyl ester;
 17 α -(2,2-Dichloro-1-methycyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -
 20 methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 17 α -(2,2-Dichlorocyclopropylcarbonyl)oxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-3-
 oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(3-methylenecyclobutylcarbonyl)oxy-3-
 oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 25 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(2-methylcyclopropylcarbonyl)oxy-3-
 oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 or a solvate of any one thereof.
13. A compound according to claim 1 which is:
- 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclobutylcarbonyl)oxy-3-oxo-
 30 androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
 or a solvate of any one thereof.

14. A compound according to claim 1 which is:
6 α ,9 α -Difluoro-17 α -(3,3-dimethylcyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
6 α ,9 α -Difluoro-17 α -(3,3-difluorocyclobutylcarbonyl)oxy-11 β -hydroxy-16 α -methyl-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
5 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -(1-methylcyclopentylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-3-oxo-17 α -(3-oxocyclobutylcarbonyl)oxy-androsta-1,4-diene-17 β -carbothioic acid S-fluoromethyl ester;
10 or a solvate of any one thereof.
15. A compound of formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable solvate thereof for use in veterinary or human medicine.
16. Use of a compound of formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable solvate thereof for the manufacture of a medicament for the treatment of inflammatory and/or allergic conditions.
15
17. A pharmaceutical composition comprising a compound of formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable solvate thereof together, if desirable, in admixture with one or more physiologically acceptable diluents or carriers.
20
18. A pharmaceutical aerosol formulation comprising a compound of formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable solvate thereof, and a fluorocarbon or hydrogen-containing chlorofluoro carbon as propellant, optionally in combination with a surfactant and or a cosolvent.
- 25 19. A pharmaceutical composition according to claim 17 which further comprises another therapeutically active agent.
20. A pharmaceutical composition according to claim 19 in which said another therapeutically active agent is a β_2 -adrenoreceptor agonist.
21. A pharmaceutical composition according to claim 20 in which said β_2 -adrenoreceptor agonist is a compound of formula (X):
30



or a salt or solvate thereof, wherein:

m is an integer of from 2 to 8;

n is an integer of from 3 to 11,

5 with the proviso that m + n is 5 to 19,

R¹¹ is -XSO₂NR¹⁶R¹⁷ wherein X is -(CH₂)_p- or C₂₋₆ alkenylene;

R¹⁶ and R¹⁷ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C(O)NR¹⁸R¹⁹, phenyl, and phenyl (C₁₋₄alkyl)-,

or R¹⁶ and R¹⁷, together with the nitrogen to which they are bonded, form a 5-, 6-, or
10 7- membered nitrogen containing ring, and R¹⁶ and R¹⁷ are each optionally substituted by one or two groups selected from halo, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, hydroxy-substituted C₁₋₆alkoxy, -CO₂R¹⁸, -SO₂NR¹⁸R¹⁹, -CONR¹⁸R¹⁹, -NR¹⁸C(O)R¹⁹, or a 5-, 6- or 7-membered heterocyclic ring;

R¹⁸ and R¹⁹ are independently selected from hydrogen, C₁₋₆alkyl,

15 C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-; and

p is an integer of from 0 to 6, preferably from 0 to 4;

R¹² and R¹³ are independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, halo, phenyl, and C₁₋₆haloalkyl; and

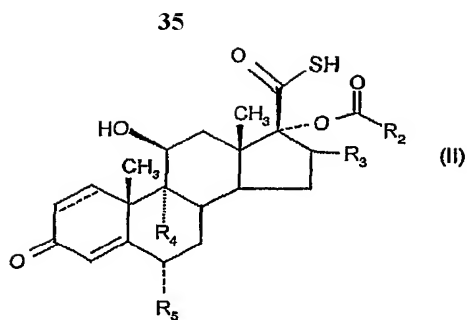
R¹⁴ and R¹⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso
20 that the total number of carbon atoms in R¹⁴ and R¹⁵ is not more than 4.

22. A pharmaceutical composition according to claim 21 in which the compound of formula (X) is 3-(4-{[6-({(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)-hexyl]oxy}butyl)benzenesulfonamide or a salt or solvate thereof.

25 23. A method for the treatment of a human or animal subject with an anti-inflammatory and/or allergic condition, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable solvate thereof.

30 24. A process for preparing a compound of formula (I) according to claim 1 which comprises alkylation of a compound of formula (II)

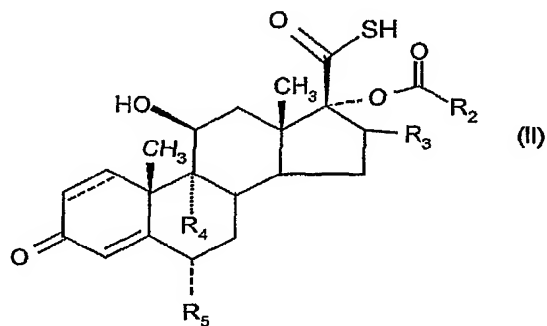
17 MAY 2001



wherein R^2 , R^3 , R^4 , R^5 and --- are as defined in claim 1.

25. A process according to claim 18 wherein alkylation is performed by reacting the compound of formula (II) with an appropriate alkyl or haloalkyl halide.

5 26. A compound of formula (II)



wherein R^2 , R^3 , R^4 , R^5 and --- are as defined in claim 1.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01971

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07J31/00 A61K31/56 A61P5/44 A61P11/06 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 335 121 A (PHILLIPPS GORDON H ET AL) 15 June 1982 (1982-06-15) column 32, line 52-65; examples 9,10,14,30 column 33, line 12-16 ---	1-26
Y	BE 889 563 A (OTSUKA PHARMA CO LTD) 3 November 1981 (1981-11-03) page 2, paragraph 2 page 64, paragraph 3 -page 65, paragraph 1 page 66, paragraph 1 page 99 --- -/--	1-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

14 August 2002

Date of mailing of the international search report

21/08/2002

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PHILLIPPS G H ET AL: "SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS IN A SERIES OF ANTIINFLAMMATORY CORTICOSTEROID ANALOGUES, HALOMETHYL ANDROSTANE-17BETA-CARBOTHIOATES AND-17BETA-CARBOSELENOATES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 22, 1 October 1994 (1994-10-01), pages 3717-3729, XP002025925 ISSN: 0022-2623 page 3722; example 13F; table 3</p> <p>---</p>	1-26
Y	<p>ISOGAI M ET AL: "BINDING AFFINITIES OF MOMETASONE FUROATE AND RELATED COMPOUNDS INCLUDING ITS METABOLITES FOR THE GLUCOCORTICOID RECEPTOR OF RAT SKIN TISSUE" JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, ELSEVIER SCIENCE LTD., OXFORD, GB, vol. 44, no. 2, 1993, pages 141-145, XP001040943 ISSN: 0960-0760 page 143; example XI page 144; table 1</p> <p>---</p>	1-26
Y	<p>US 4 113 680 A (KAMANO YOSHIAKI ET AL) 12 September 1978 (1978-09-12) page 2, line 34-38, 51-56; examples 7, 24, 73, 83, 104G, 108C, 113, 141, 156, 194, 219</p> <p>---</p>	1-26
Y	<p>UENO H ET AL: "Synthesis and evaluation of antiinflammatory activities of a series of corticosteroid 17.alpha.-esters containing a functional group" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 34, no. 8, 1 August 1991 (1991-08-01), pages 2468-2473, XP002086576 ISSN: 0022-2623 page 2470; example 13I; table II page 2471, column 1, paragraph 1</p> <p>---</p>	1-26
Y	<p>US 3 312 590 A (JOSEPH ELKS ET AL) 4 April 1967 (1967-04-04) column 1, line 15-27; example 8</p> <p>---</p>	1-26
Y	<p>US 3 639 434 A (OXLEY PETER ET AL) 1 February 1972 (1972-02-01) column 1, line 49-57; examples 1, 19</p> <p>---</p> <p>--- -/--</p>	1-26

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3 557 162 A (MARX ARTHUR F ET AL) 19 January 1971 (1971-01-19) page 3, line 44-50; example VI -----	1-26
Y	US 3 891 631 A (PHILLIPPS GORDON HANLEY ET AL) 24 June 1975 (1975-06-24) column 1, line 6-14 column 5, line 10 -----	1-26
P, Y	WO 02 00679 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); BEATTIE DAVID (GB)) 3 January 2002 (2002-01-03) page 7, last paragraph -page 8, last paragraph; claim 1; examples 8,9,12,14,24,32,34 -----	1-26

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 23 IS directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01971

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4335121	A	15-06-1982	AT 395428 B	28-12-1992
			AT 17084 A	15-05-1992
			AT 401521 B	25-09-1996
			AT 34491 A	15-02-1996
			AT 395427 B	28-12-1992
			AT 67481 A	15-05-1992
			AT 395429 B	28-12-1992
			AT 203186 A	15-05-1992
			AU 544517 B2	06-06-1985
			AU 6729881 A	20-08-1981
			BE 887518 A1	13-08-1981
			BG 60700 B2	29-12-1995
			CA 1201114 A1	25-02-1986
			CA 1205464 C	03-06-1986
			CH 644615 A5	15-08-1984
			CH 651307 A5	13-09-1985
			CZ 9104034 A3	16-03-1994
			CY 1291 A	18-10-1985
			DE 3105307 A1	10-12-1981
			DE 3153379 C2	19-11-1992
			DK 62381 A ,B,	16-08-1981
			ES 499394 D0	01-09-1982
			ES 8207194 A1	01-12-1982
			ES 509539 D0	01-04-1983
			ES 8305379 A1	01-07-1983
			ES 518161 D0	16-01-1984
			ES 8402317 A1	16-04-1984
			ES 524985 D0	01-01-1985
			ES 8502447 A1	01-04-1985
			ES 532055 D0	16-10-1985
			ES 8600936 A1	16-02-1986
			FI 810444 A ,B,	16-08-1981
			FR 2477156 A1	04-09-1981
			FR 2485542 A1	31-12-1981
			GB 2088877 A ,B	16-06-1982
			GB 2137206 A ,B	03-10-1984
			HK 58385 A	16-08-1985
			IE 51394 B1	24-12-1986
			IE 51395 B1	24-12-1986
			IT 1170717 B	03-06-1987
			JP 1488353 C	23-03-1989
			JP 56138200 A	28-10-1981
			JP 63037120 B	22-07-1988
			KE 3526 A	07-06-1985
			KR 8500969 B1	02-07-1985
			MX 9202717 A1	30-06-1992
			MY 75785 A	31-12-1985
			NL 84649 C	
			NL 8100707 A ,B,	16-09-1981
			NZ 196260 A	30-11-1983
BE 889563	A	03-11-1981	AT 379817 B	10-03-1986
			AT 265684 A	15-07-1985
			AT 379816 B	10-03-1986
			AT 307081 A	15-07-1985
			AU 540898 B2	06-12-1984
			AU 7259181 A	14-01-1982
			BE 889563 A1	03-11-1981

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
BE 889563	A	CA 1174667 A1	18-09-1984
		CH 648856 A5	15-04-1985
		DE 3126732 A1	25-03-1982
		DK 302181 A ,B,	11-01-1982
		ES 504340 D0	01-12-1982
		ES 8300785 A1	01-02-1983
		ES 514633 D0	16-06-1983
		ES 8306767 A1	16-09-1983
		FI 812175 A ,B,	11-01-1982
		FR 2486529 A1	15-01-1982
		GB 2079755 A ,B	27-01-1982
		IT 1205446 B	23-03-1989
		JP 1011037 B	23-02-1989
		JP 1530924 C	15-11-1989
		JP 57045200 A	13-03-1982
		KR 8600266 B1	22-03-1986
		NL 8103315 A ,B,	01-02-1982
		NO 812344 A ,B,	11-01-1982
		PH 25874 A	02-12-1991
		PT 73348 A ,B	01-08-1981
		SE 449106 B	06-04-1987
		SE 8104132 A	11-01-1982
		SU 1318169 A3	15-06-1987
		US 4710495 A	01-12-1987
		US 4996335 A	26-02-1991
		ZA 8104440 A	27-10-1982
US 4113680	A	12-09-1978	JP 1030580 C
			22-01-1981
			JP 51125372 A
			01-11-1976
			JP 55021758 B
			12-06-1980
			JP 1030583 C
			22-01-1981
			JP 51128954 A
			10-11-1976
			JP 55021759 B
			12-06-1980
			CA 1044225 A1
			12-12-1978
			CH 609709 A5
			15-03-1979
			DE 2613875 A1
			14-10-1976
			DK 144076 A ,B,
			01-10-1976
US 3312590	A	04-04-1967	ES 446411 A1
			01-02-1979
			FR 2306214 A1
			29-10-1976
			GB 1508517 A
			26-04-1978
			HU 174850 B
			28-03-1980
			IN 142583 A1
			30-07-1977
			NL 7603249 A
			04-10-1976
			PT 64885 A ,B
			01-04-1976
			SE 403380 B
			14-08-1978
			SE 7603791 A
			01-10-1976
			YU 54476 A1
			31-05-1982
			GB 1047518 A
			02-11-1966
			BE 649170 A
			11-12-1964
			BE 649171 A
			11-12-1964
			CH 450410 A
			31-01-1968
			CH 457422 A
			15-06-1968
			DE 1443957 A1
			02-01-1970
			DE 1443958 A1
			02-01-1970
			DK 116205 B
			22-12-1969
			DK 116128 B
			15-12-1969
			FR 4548 M

INTERNATIONAL SEARCH REPORT

PCT/GB 02/01971

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3312590	A		MY 13170 A	31-12-1970
			NL 6406614 A ,B	14-12-1964
			NL 6406615 A ,B	14-12-1964
			NO 125532 B	25-09-1972
			NO 125533 B	25-09-1972
			SE 320066 B	02-02-1970
			SE 313562 B	18-08-1969
US 3639434	A	01-02-1972	US 3856956 A	24-12-1974
US 3557162	A	19-01-1971	AT 292929 B	15-08-1971
			BE 726981 A	16-07-1969
			CH 511822 A	31-08-1971
			DE 1903118 A1	07-08-1969
			DK 120234 B	03-05-1971
			ES 362475 A1	01-12-1970
			FR 8225 M	28-09-1970
			FR 2000571 A5	12-09-1969
			GB 1227992 A	15-04-1971
			IT 1036015 B	30-10-1979
			NL 6901024 A ,B,	25-07-1969
			SE 339828 B	25-10-1971
US 3891631	A	24-06-1975	GB 1440063 A	23-06-1976
			AU 5914373 A	13-02-1975
			BE 803461 A1	11-02-1974
			CA 1027109 A1	28-02-1978
			CH 590884 A5	31-08-1977
			DE 2340591 A1	07-03-1974
			DK 135998 B	25-07-1977
			ES 417738 A1	16-06-1976
			FR 2205508 A1	31-05-1974
			IE 38312 B1	15-02-1978
			IL 42942 A	31-05-1977
			JP 1159031 C	25-07-1983
			JP 49085062 A	15-08-1974
			JP 57052359 B	06-11-1982
			LU 68212 A1	16-10-1973
			NL 7311072 A	13-02-1974
			SE 387951 B	20-09-1976
			ZA 7305452 A	31-07-1974
			ZA 7305453 A	30-10-1974
WO 0200679	A	03-01-2002	AU 8389101 A	08-01-2002
			WO 0200679 A2	03-01-2002